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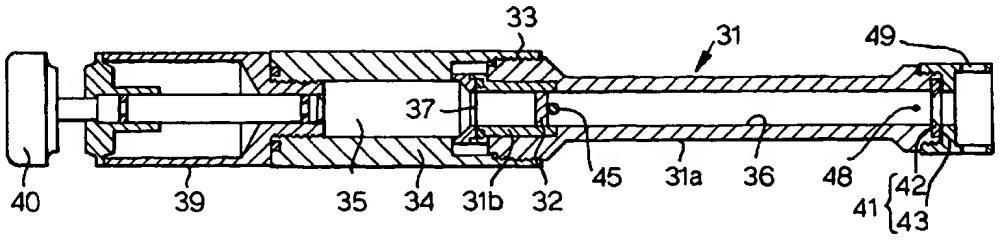
(54) Title: NEEDLELESS SYRINGE



(57) Abstract: A needleless syringe is disclosed for use in delivering a particle into target tissues of a subject. The syringe comprises a barrel (31) and a macroprojectile (32) received in the barrel (31). A downstream side of the macroprojectile (32) carries the particle (45) to be delivered. A macroprojectile arresting device (41) is arrested at the downstream end of the barrel to arrest movement of the macroprojectile (32). An energy source is provided for accelerating the macroprojectile along the bore (36) of the barrel (31), to cause the particle (45) to be launched from the syringe as movement of the macroprojectile (32) is arrested by the arresting device (41). The macroprojectile (32) may be injection moulded in a polyolefin material. In addition, the downstream side of the macroprojectile (32) may be either provided with a plurality of bristles (20) to assist retention of the particle, or provided with a plated surface to assist separation of the particle. The macroprojectile arresting device (41) may be provided with a cushioning portion (43) to cushion deceleration of the macroprojectile (32). The barrel (31) may comprise an upstream portion (31b) and a downstream portion (31a), with the upstream portion (31b) being separable from the downstream portion (31a). This upstream barrel portion (31b), together with the macroprojectile (32), can thus from a removable cartridge (44) to enable ready replacement of a spent cartridge with a fresh cartridge.

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NEEDLELESS SYRINGE

TECHNICAL FIELD

This invention relates to needleless syringes for use in delivering a particle into target tissue of a subject. Said particle may, for example, comprise a drug, vaccine, diagnostic agent or carrier particle coated with a genetic material (or any combination thereof).

BACKGROUND OF THE INVENTION

The ability to deliver pharmaceuticals through skin surfaces (transdermal delivery) provides many advantages over oral or parenteral delivery techniques. In particular, transdermal delivery provides a safe, convenient and noninvasive alternative to traditional drug administration systems, conveniently avoiding the major problems associated with oral delivery (e.g. variable rates of absorption and metabolism, gastrointestinal irritation and/or bitter or unpleasant drug tastes) or parenteral delivery (e.g. needle pain, the risk of introducing infection to treated individuals, the risk of contamination or infection of health care workers caused by accidental needle-sticks and the disposal of used needles). In addition, transdermal delivery affords a high degree of control over blood concentrations of administered pharmaceuticals.

Recently, a novel transdermal drug delivery system that entails the use of a needleless syringe to fire powders (i.e. solid drug-containing particles) in controlled doses into and through intact skin has been described. In particular, US Patent No. 5,630,796 to Bellhouse et al. describes a needleless syringe that delivers pharmaceutical particles entrained in a supersonic gas flow. The needleless syringe is used for transdermal delivery of powdered drug compounds and compositions, for delivery of genetic material into living cells (e.g. gene therapy) and for the delivery of biopharmaceuticals to skin, muscle, blood or lymph. The needleless syringe can also be used in conjunction with surgery to deliver drugs and biologics to organ surfaces, solid tumours and/or to surgical cavities (e.g. tumour beds or cavities after tumour resection). In theory, practically any pharmaceutical agent that can be prepared in a substantially solid, particulate form can be safely and easily delivered

using such devices.

One needleless syringe described in US Patent No. 5,630,796. comprises an elongate tubular converging-diverging nozzle having a rupturable membrane initially closing the passage through the nozzle and arranged substantially adjacent to the upstream end of the nozzle. Particles of a therapeutic agent to be delivered are disposed adjacent to the rupturable membrane and are delivered using an energizing means which applies a gaseous pressure to the upstream side of the membrane sufficient to burst the membrane and produce a supersonic gas flow (containing the pharmaceutical particles) through the nozzle for delivery from the downstream end thereof. The particles can thus be delivered from the needleless syringe at very high velocities which are readily obtainable upon the bursting of the rupturable membrane. The passage through the nozzle has an upstream convergent portion, leading through a throat to a downstream, divergent portion. The converging-diverging passage is used to accelerate the gas to supersonic speed. The gas is first brought to Mach 1 in the throat and the downstream divergence accelerates it to a steady state supersonic speed.

With the syringes described in US Patent No. 5,630,796 particles can be delivered at a large range of velocities with potentially non-uniform spatial distribution across the target surface. A variation in particle velocity can make it difficult to deliver high-potency powdered drugs, vaccines etc to specific target layers within the skin. Furthermore, non-uniform spatial distribution can cause problems which would be ameliorated if a more even spatial distribution could be achieved.

A further design of needleless syringe has been described in WO 96/20022 to Bellhouse et al. In this second case the needleless syringe comprises a body containing a lumen, an upstream end of which is, or is arranged to be, connected to a source of gaseous pressure. The downstream end of the lumen terminates behind a diaphragm which is movable outwardly from an inverted first position, in which it presents outwardly of the body a concavity for containing particles of a therapeutic agent, to a second position. The diaphragm, in both its first and second positions, is sealably secured around its periphery to the downstream end of the lumen. The

arrangement is such that, in use, when gas under pressure is suddenly released into the lumen, the diaphragm will move outwardly from its first position to its second position and catapult the particles outwardly. Although the positioning of particles on the movable diaphragm can give a fairly uniform spatial distribution across the target surface, as a result of the complex and non-uniform mechanisms of the movable diaphragm, for example arising from the centre of the diaphragm being less restrained and thus capable of moving through a bigger distance than areas of the diaphragm towards its periphery, non-uniform particle velocities can be achieved at the target surface.

US Patent No. 4,945,050 to Sanford et al discloses an apparatus for accelerating particles, comprising a large mass macroprojectile containing the particles, means for accelerating the macroprojectile and stopping means for stopping the macroprojectile thereby displacing the particles from the macroprojectile and propelling them toward a target. In one embodiment disclosed in US Patent No. 4,945,050 the macroprojectile is a nylon macroprojectile.

The large mass of the macroprojectile disclosed in US Patent No. 4,945,050 not only requires high driver pressures and volumes to achieve the desired macroprojectile velocity, but the large macroprojectile mass can mean that the decelerating forces acting on the macroprojectile upon its impaction with the stopping means are massive, leading to problems with macroprojectile fracture. If an apparatus comprising, inter alia, a macroprojectile is to be used to deliver a particle into target tissue of a subject, the possibility of macroprojectile fracture cannot be tolerated as there is a risk that a fractured portion of the macroprojectile could pass out through the end of the apparatus to impact the target tissue, risking damage.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided a needleless syringe for use in delivering a particle into target tissue of a subject, the syringe comprising:

an elongate, tubular barrel having upstream and downstream ends;

a macroprojectile received in the tubular barrel, said macroprojectile having a downstream side adapted to carry the particle to be delivered;

a macroprojectile arresting device provided at the downstream end of the barrel to arrest movement of the macroprojectile; and

an energy source for accelerating the macroprojectile along the barrel in the downstream direction upon operation of the syringe to cause the particle to be launched from the syringe when movement of the macroprojectile is arrested by the macroprojectile arresting device,

wherein said macroprojectile is injection moulded in a plastics material.

According to a second aspect of the present invention there is provided a needleless syringe for use in delivering a particle into target tissue of a subject, the syringe comprising:

an elongate, tubular barrel having upstream and downstream ends;

a macroprojectile received in the tubular barrel, said macroprojectile having a downstream side adapted to carry the particle to be delivered;

a macroprojectile arresting device provided at the downstream end of the barrel to arrest movement of the macroprojectile; and

an energy source for accelerating the macroprojectile along the barrel in the downstream direction upon operation of the syringe to cause the particle to be launched from the syringe when movement of the macroprojectile is arrested by the macroprojectile arresting device,

wherein the downstream side of the macroprojectile either comprises a plurality of bristles to assist retention of the particle on the downstream side of the macroprojectile, comprises a plated surface to assist separation of the particle from the downstream side of the macroprojectile, or comprises both said bristles and said plated surface.

According to an embodiment of the present invention there is provided a needleless syringe for use in delivering a particle into target tissue of a subject, the syringe comprising:

an elongate, tubular barrel having upstream and downstream ends;

a macroprojectile received in the tubular barrel, said macroprojectile having a downstream side adapted to carry the particle to be delivered;

a macroprojectile arresting device provided at the downstream end of the

barrel to arrest movement of the macroprojectile; and

an energy source for accelerating the macroprojectile along the barrel in the downstream direction upon operation of the syringe to cause the particle to be launched from the syringe when movement of the macroprojectile is arrested by the macroprojectile arresting device,

wherein the macroprojectile arresting device is provided with a cushioning portion to cushion deceleration of the macroprojectile upon its impact with the macroprojectile arresting device.

According to a third aspect of the present invention there is provided a needleless syringe for use in delivering a particle into target tissue of a subject, the syringe comprising:

an elongate, tubular barrel having upstream and downstream ends;

a macroprojectile received in the tubular barrel, said macroprojectile having a downstream side adapted to carry the particle to be delivered;

a macroprojectile arresting device provided at the downstream end of the barrel to arrest movement of the macroprojectile; and

an energy source for accelerating the macroprojectile along the barrel in the downstream direction upon operation of the syringe to cause the particle to be launched from the syringe when movement of the macroprojectile is arrested by the macroprojectile arresting device,

wherein the barrel comprises an upstream portion and a downstream portion, the upstream portion being separable from the downstream portion, and further wherein the macroprojectile is provided in the form of a removable cartridge comprising at least the macroprojectile and the upstream barrel portion.

According to a fourth aspect of the present invention there is provided a cartridge for use in a needleless syringe, said cartridge comprising:

a cartridge barrel section having a bore;

a macroprojectile received in the bore of the cartridge barrel section; and

a particle releasably carried on a downstream face of the macroprojectile.

In the hereinafter described and illustrated embodiments of needleless syringe in accordance with the present invention, a particle to be delivered is carried on a

macroprojectile which is, in use, accelerated along a barrel of finite length. The macroprojectile arresting device arrests progress of the macroprojectile whilst the particle formerly carried on the macroprojectile continues on towards the target surface. Because the macroprojectile acceleration and deceleration is not reliant upon macroprojectile deformation to any significant degree (unlike in the device disclosed in WO 96/20022 to Bellhouse et al), when a plurality of particles are carried by the macroprojectile those particles are delivered at uniform velocities, with a highly uniform spatial distribution of those particles across the target surface. Furthermore, the acceleration forces imparted on the particle are two orders of magnitude less than those imparted in the prior art device disclosed in the above-mentioned US Patent No. 5 630 796 to Bellhouse et al, reducing the possibility of particle attrition before impact with the target. A further advantage is that, because the distance over which the macroprojectile travels is high, for example compared with the range of diaphragm movement possible in the device disclosed in WO 96/20022 to Bellhouse et al, the particle may be accelerated over a long distance; enabling higher particle velocities to be achieved for a given size of energy source.

BRIEF DESCRIPTION OF FIGURES

Embodiments of syringe in accordance with the present invention will now be described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 is a sectional side elevation of a first embodiment of needleless syringe in accordance with the present invention;

Figures 2A and 2B are top plan and side views, respectively, of a macroprojectile provided on its downstream side with three integrally moulded sets of bristles;

Figures 3A and 3B are top plan and side views, respectively, of a macroprojectile provided on its downstream side with a single integrally moulded sets of bristles;

Figure 4 is a sectional side elevation of a second embodiment of needleless syringe in accordance with the present invention;

Figures 5A, 5B and 5C are sectional side elevations of three variants of

macroprojectile suitable for use in either of the Figure 1 and Figure 4 needleless syringes (to a different scale);

Figure 6 is a sectional side elevation of a cartridge for use in the needleless syringe of Figure 4 (to a different scale); and

Figure 7 is a plot of particle and piston velocities obtained with the second embodiment of needleless syringe, for different diaphragm thicknesses and driver chamber pressures.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular pharmaceutical formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entirety.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a therapeutic agent" includes a mixture of two or more such agents, reference to "a gas" includes mixtures of two or more gases, and the like.

A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

The following terms are intended to be defined as indicated below.

The term "needleless syringe," as used herein, expressly refers to a particle delivery system that can be used to deliver particles into and/or across tissue, wherein the particles may have an average size ranging from about 0.1 to 250 μm, preferably about 10-70 μm. Particles larger than about 250 μm can also be delivered from these devices, with the upper limitation being the point at which the size of the particles would cause untoward pain and/or damage to the target tissue. The particles may be

delivered at high velocity, for example at velocities of at least about 150 m/s or more, and more typically at velocities of about 250-300 m/s or greater. Such needleless syringes were first described in commonly-owned U.S. Patent No. 5,630,796 to Bellhouse et al., incorporated herein by reference, and have since been described in commonly owned International Publication Nos. WO 96/04947, WO 96/12513, and WO 96/20022, all of which publications are also incorporated herein by reference. These devices can be used in the transdermal delivery of a therapeutic agent into target skin or mucosal tissue, either *in vitro* or *in vivo* (*in situ*); or the devices can be used in the transdermal delivery of generally inert particles for the purpose of non- or minimally invasive sampling of an analyte from a biological system. Since the term only relates to devices which are suitable for delivery of particulate materials, devices such as liquid-jet injectors are expressly excluded from the definition of a "needleless syringe."

The term "particle", as used herein, covers a single particle as well as plural particles.

The term "transdermal" delivery captures intradermal, transdermal (or "percutaneous") and transmucosal administration, i.e., delivery by passage of a therapeutic agent into and/or through skin or mucosal tissue. See, e.g., *Transdermal Drug Delivery: Developmental Issues and Research Initiatives*, Hadgraft and Guy (eds.), Marcel Dekker, Inc., (1989); *Controlled Drug Delivery: Fundamentals and Applications*, Robinson and Lee (eds.), Marcel Dekker Inc., (1987); and *Transdermal Delivery of Drugs*, Vols. 1-3, Kydonieus and Berner (eds.), CRC Press, (1987). Aspects of the invention which are described herein in the context of "transdermal" delivery, unless otherwise specified, are meant to apply to intradermal, transdermal and transmucosal delivery. That is, the present invention, unless explicitly stated otherwise, should be presumed to be equally applicable to intradermal, transdermal and transmucosal modes of delivery.

As used herein, the terms "therapeutic agent" and/or "particles of a therapeutic agent" intend any compound or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic, immunogenic, and/or physiologic effect by local and/or systemic action. The term

therefore encompasses those compounds or chemicals traditionally regarded as drugs, vaccines, and biopharmaceuticals including molecules such as proteins, peptides, hormones, biological response modifiers, nucleic acids, gene constructs and the like. More particularly, the term "therapeutic agent" includes compounds or compositions for use in all of the major therapeutic areas including, but not limited to, adjuvants, anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; local and general anesthetics; anorexics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antigens, antihistamines; anti-inflammatory agents; antinauseants; antineoplastics; antipruritics; antipsychotics; antipyretics; antispasmodics; cardiovascular preparations (including calcium channel blockers, beta-blockers, beta-agonists and antiarrythmics); antihypertensives; diuretics; vasodilators; central nervous system stimulants; cough and cold preparations; decongestants; diagnostics; hormones; bone growth stimulants and bone resorption inhibitors; immunosuppressives; muscle relaxants; psychostimulants; sedatives; tranquilizers; proteins peptides and fragments thereof (whether naturally occurring, chemically synthesized or recombinantly produced); and nucleic acid molecules (polymeric forms of two or more nucleotides, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) including both double- and single-stranded molecules, gene constructs, expression vectors, antisense molecules and the like).

Particles of a therapeutic agent, alone or in combination with other drugs or agents, are typically prepared as pharmaceutical compositions which can contain one or more added materials such as carriers, vehicles, and/or excipients. "Carriers," "vehicles" and "excipients" generally refer to substantially inert materials which are nontoxic and do not interact with other components of the composition in a deleterious manner. These materials can be used to increase the amount of solids in particulate pharmaceutical compositions. Examples of suitable carriers include water, silicone, gelatin, waxes, and like materials. Examples of normally employed "excipients," include pharmaceutical grades of dextrose, sucrose, lactose, trehalose, mannitol, sorbitol, inositol, dextran, starch, cellulose, sodium or calcium phosphates, calcium sulfate, citric acid, tartaric acid, glycine, high molecular weight polyethylene glycols (PEG), and combinations thereof. In addition, it may be desirable to include

a charged lipid and/or detergent in the pharmaceutical compositions. Such materials can be used as stabilizers, anti-oxidants, or used to reduce the possibility of local irritation at the site of administration. Suitable charged lipids include, without limitation, phosphatidylcholines (lecithin), and the like. Detergents will typically be a nonionic, anionic, cationic or amphoteric surfactant. Examples of suitable surfactants include, for example, Tergitol® and Triton® surfactants (Union Carbide Chemicals and Plastics, Danbury, CT), polyoxyethylenesorbitans, e.g., TWEEN® surfactants (Atlas Chemical Industries, Wilmington, DE), polyoxyethylene ethers, e.g., Brij, pharmaceutically acceptable fatty acid esters, e.g., lauryl sulfate and salts thereof (SDS), and like materials.

The term "analyte" is used herein in its broadest sense to denote any specific substance or component that one desires to detect and/or measure in a physical, chemical, biochemical, electrochemical, photochemical, spectrophotometric, polarimetric, colorimetric, or radiometric analysis. A detectable signal can be obtained, either directly or indirectly, from such a material. In some applications, the analyte is a physiological analyte of interest (e.g., a physiologically active material), for example glucose, or a chemical that has a physiological action, for example a drug or pharmacological agent.

As used herein, the term "sampling" means extraction of a substance, typically an analyte, from any biological system across a membrane, generally across skin or tissue.

B. General Methods

Fig. 1 shows a first embodiment of needleless syringe in accordance with the present invention, suitable for use in delivering a particle into target tissue of a subject.

The syringe comprises an elongate, tubular barrel 1 having an upstream end (to the left as drawn) and a downstream end and a polished central bore 6, for example of 10 mm diameter. The tubular barrel 1 may be made of metal, but is preferably moulded in a structural plastics material, for example polyurethane, polyethylene, polypropylene or other suitable plastics materials.

Slidably received in the region of the upstream end of the tubular barrel is a

macroprojectile 2. This macroprojectile 2 has a downstream side (the right hand side as drawn) adapted to carry the particle (not shown) to be delivered.

The macroprojectile is preferably made substantially from a polyolefin material selected for its mechanical and physical parameters (mainly tensile strength and good high temperature properties), for example a copolymer or homopolymer formed from a polyethylene or polypropylene material, including high-density polyethylene, low density polyethylene, medium density polyethylene and linear low-density polyethylene. The copolymers may be random or block copolymers. Other structural plastics material may also be suitable. The physical properties of the material should be such as to avoid the macroprojectile shattering when subjected to extreme acceleration and deceleration forces, as will be described below. In the illustrated embodiment the macroprojectile 2 has a mass of 163 mg.

The preferred technique for manufacturing the macroprojectile is to injection mould it. This has advantages over machining the macroprojectile as machining it can give rise to stress raisers in the macroprojectile, making the macroprojectile more susceptible to fracture when undergoing extreme deceleration. Furthermore, machined macroprojectiles are relatively time consuming to manufacture within the closely desired tolerance required for predictable performance.

In the illustrated embodiment the exterior of the upstream end of the tubular barrel 1 is provided with a thread 3, to enable the tubular barrel 1 to be threadedly attached to a driver portion 4 defining therein a driver chamber 5. Other suitable attachments are, of course, also available such as snap-fit locks, luer-type locks, detents and the like. Once again, the driver portion 4 may be made of metal but is advantageously moulded in a structural plastics material.

In order to provide a rush of pressurized gas from the driver chamber 5 into the upstream end of the bore 6 provided in the tubular barrel 1, in the illustrated embodiment a rupturable membrane 7 is sandwiched, around its periphery, between an annular spacer element 8 and the shoulder of a recess provided at the upstream end of the tubular barrel 1. The sandwiching pressure is provided by the action of screwthreading the driver portion 4 onto the threads 3 provided at the upstream end of the tubular barrel 1.

The rupturable membrane 7 may be made of any suitable material, for example aluminium, polycarbonate, steel or Mylar and the construction of the rupturable membrane chosen to give the membrane a predetermined rupture pressure, i.e. pressure in the driver chamber 5, at which the membrane 7 will rupture. As will be described below, by changing the thickness and/or material type of the membrane 7 the rupture pressure of this membrane, and thus the particle delivery characteristics of the syringe, can be adjusted.

Attached to the driver portion 4 at its upstream end is an energy source for use in accelerating the macroprojectile 2 along the bore 6 of the barrel 1 in the downstream direction upon operation of the syringe. Attachment can be by any suitable means, for example, using threaded coupling (as shown in Fig. 1), or snap-fit, luer lock or detent couplers. In the illustrated embodiment this energy source takes the form of a high pressure gas reservoir 9, filled with helium or another suitable gas, made from metal. The pressurized gas contained within the reservoir 9 can be released into the driver chamber 5 by pushing the button 10 (to the right as drawn). The reservoir 9 may have a construction and method of operation similar to the corresponding reservoir of the needleless syringe disclosed in US Patent No. 5,630,796, the contents of which are hereby incorporated by way of reference.

Although in the illustrated embodiment the energy source takes the form of a gas reservoir 9 operated via a push button 10, the energy source might alternatively be a one-shot gas reservoir whose neck is fractured to release gas, an explosive charge which is detonated to release rapidly a large volume of gas or even a mechanical energy storing device, such as a spring which may be used to store energy which, upon release, can be used to drive the macroprojectile 2. Where the energy source is a gas reservoir, the macroprojectile preferably has a mass in the range of 0.5 to 1.5 times the mass of compressed gas in the reservoir.

A macroprojectile arresting device 11 is provided at the downstream end of the tubular barrel 1. In the illustrated embodiment this device 11 takes the form of a relatively rigid annular stopping plate and an annular cushioning plate 13 to be compressed by the stopping plate upon macroprojectile impact. Both the stopping plate 12 and the cushioning plate 13 define a central aperture therein for the passage

therethrough of the particle carried by the macroprojectile, the size of this central aperture being smaller than the diameter of the macroprojectile 2.

In the illustrated embodiment the macroprojectile arresting device is removable from the downstream end of the tubular barrel 1 by virtue of the provision of cooperating threads on the stopping plate 12 and the tubular barrel 1.

Although in the illustrated embodiment the stopping plate 12 and cushioning plate 13 are distinct members, they may be integral. In other words, the whole macroprojectile arresting device 11 might, for example, be moulded in a single structural plastics material.

Where the stopping plate 12 and cushioning plate 13 are different items, it is intended that the cushioning plate 13 should be made of a material which is softer than the relatively rigid material of the stopping plate 12, so as to cushion deceleration of the macroprojectile 2 upon its impact with the macroprojectile arresting device 11, ideally an elastomeric material or a non-elastomeric material with similar properties to an elastomeric material. In such a situation, the stopping plate 12 could be engineered to provide the strength to resist the macroprojectile passing out of the syringe completely, with the cushioning plate 13 being provided to cushion macroprojectile deceleration. When, however, the stopping plate 12 and cushion plate 13 are integrally formed, for example by choosing a material that is appropriately strong and appropriately soft, both characteristics may be provided by a macroprojectile arresting device 11 comprising a single structural element, for example a single element moulded in a structural plastics material.

In order to facilitate delivery of the particle on the downstream side of the macroprojectile 2, the downstream side of a macroprojectile may be provided with some means for affecting particle retention. For example, the downstream side of the macroprojectile 2 might be provided with one or more topographical features to selectively retain a particle thereon, in the manner disclosed in International Patent Application No. PCT/GB00/00932, the contents of which are hereby incorporated by way of reference. Such topographical features may comprise a plurality of bristles extending therefrom generally in the downstream direction. Figures 2A and 2B show a macroprojectile whose downstream side is provided with three integrally moulded

sets of bristles 20, the bristles of each set being arranged approximately in a circle. Between the bristles of each set an individual particle is held by virtue of the lateral displacement of the elastic bristles. Figures 3A and 3B show a macroprojectile whose downstream surface is provided with a single set of bristles, which bristles are arranged in a circle of greater diameter to accommodate a larger particle. The provision of bristles helps to securely retain on the macroprojectile particles greater than 0.2 mm in diameter, by retaining these particles between the bristles. Particles smaller than 0.2 mm in diameter are less securely retained by bristles, but can still withstand forces of about 2 g.

Alternatively or additionally, the downstream side of the macroprojectile 2 may be provided with a plated surface, preferably a gold plated surface. The natural adhesion of gold particles (for example of 3 μm in diameter) to a polyolefin macroprojectile is usually too strong to enable the gold particles to be delivered from the needleless syringe. This natural adhesion can be dramatically reduced by providing the downstream surface of the macroprojectile with gold plating, for example by using a sputtering technique, enhancing particle delivery. Where the particle is to be delivered is a gold carrier particle, for example coated with genetic material, the provision of a gold plated surface on the downstream face of the macroprojectile 2 has been found to reduce sufficiently the natural adhesion of gold particles to plastics materials so as to enable the gold particles to be delivered by a plastics material macroprojectile.

The macroprojectile 2 employed in the first embodiment of syringe may have the general construction illustrated in any of Figures 2A, 2B, 3A and 3B.

To operate the first embodiment of needleless syringe the following procedure can be followed.

With the driver portion 4 and tubular barrel 1 separated, a rupturable membrane 7 is positioned in the recess formed at the upstream end of the tubular barrel 1, together with the annular spacer element 8, and the driver portion 4 and tubular barrel 1are screwed together to clamp the rupturable membrane 7 around its periphery.

Prior to screwing the driver portion 4 and tubular barrel 1 together, the

macroprojectile 2 (with the particle to be delivered carried on its downstream surface) may have been placed in the position shown in Fig. 1 through the upstream end of the bore 6 in the tubular barrel 1. Alternatively, after the driver portion 4 and tubular barrel 1 have been screwed together, the macroprojectile 2 can be inserted into position from the downstream end of the tubular barrel 1. If the latter option is followed, the macroprojectile arresting device 11 will obviously need to be detached from the tubular barrel 1 at the time of insertion of the macroprojectile 2. In this case, after loading the macroprojectile 2 from the downstream end of the tubular barrel 1, the macroprojectile arresting device 11 would need to be attached to the downstream end of the tubular barrel 1 by positioning the cushioning plate 13 against the flat surface at the downstream end of the tubular barrel and then threading the stopping plate 12 onto the downstream end of the tubular barrel 1.

In the illustrated embodiment the reservoir 9 is attached to the driver portion 4 via a screw thread. The interior of the reservoir 9 would be filled with pressurized gas, for example helium, and the reservoir 9 attached to the driver portion 4 via cooperating screw threads. In this situation, the driver chamber 5 would be filled with air at atmospheric pressure. By depressing the button 10 the driver chamber 5 will fill with helium (or whatever other gas was charged in the reservoir 9). When the pressure within the driver chamber 5 reaches the rupture pressure of the rupturable membrane 7 the membrane 7 will rupture and the gas within the driver chamber 5 will expand to do work on the macroprojectile 2, accelerating it along the bore 6 of the tubular barrel 1 until the macroprojectile impacts the macroprojectile arresting device 11, whereupon the macroprojectile 2 will be rapidly decelerated and the particle carried on the downstream side of the macroprojectile will be launched through the central aperture of the macroprojectile arresting device 11 to impact into a target surface, against which the downstream face of the macroprojectile arresting device 11 has been previously contacted or placed in close proximity to. The particle may, as mentioned above, be of a therapeutic agent, and may or may not comprise a carrier particle.

With a macroprojectile mass of 163 mg, readings of terminal macroprojectile velocity were taken at different rupture pressures for the rupturable membrane 7. At

the following approximate membrane rupture pressures (in bar), the following approximate terminal macroprojectile velocities were achieved: 190 m/s (11 bar); 230 m/s (19 bar); 250 m/s (22 bar); 300 m/s (27 bar).

A second embodiment of needleless syringe is illustrated in Fig. 4.

The main differences between the Fig. 1 and Fig. 4 embodiments reside in the macroprojectile/rupturable membrane and in the macroprojectile arresting device. The driver portion 34, driver chamber 35, reservoir 39 and push button 40 in the Fig. 4 embodiment are generally similar to the Figure 1 embodiment.

The overall length of the device illustrated in Fig. 4 is 165 mm, with the bore 36 of the tubular barrel 31 being 6 mm. This is smaller than the bore of the Fig. 1 embodiment, which enables a smaller, lighter macroprojectile 32 to be used. By enabling the use of an even more lightweight macroprojectile (for example 35 mg, in contrast to the 163 mg of the macroprojectile of the first embodiment), the macroprojectile can be made to accelerate very rapidly to a high speed (for example of the order of 400 m/s). Additionally, the energy required to accelerate a lightweight macroprojectile is less, reducing the gas requirement by requiring less gas at a lower pressure, allowing the whole syringe to be made more compact and to be safer to use. Furthermore, the stresses involved in decelerating the macroprojectile will be reduced, reducing the likelihood of the macroprojectile 32 shattering or yielding when its progress is arrested by the macroprojectile arresting device 41, contributing to the safety of the syringe.

In the Fig. 4 arrangement the reservoir 39 has a capacity of approximately 4.4 ml, containing helium gas at a pressure of approximately 65 bar. This helium gas charge has been found to be sufficient to accelerate the macroprojectile 32 of the Fig. 4 embodiment to a final velocity of approximately 400 m/s, subjecting the macroprojectile 32 to a deceleration of the order of 10^8 m/s^2. The capacity of the reservoir 9, 39 is advantageously less than 5 times the volume of the tubular barrel swept by the macroprojectile, ideally less than 2 times.

The basic preferred macroprojectile design in the Fig. 4 embodiment is shown more clearly in Fig. 5A. The macroprojectile 32 is 2 mm deep overall with the upstream side of the macroprojectile provided with a 1 mm deep recess of 5 mm

diameter in its centre to provide the upstream side of the macroprojectile with a generally annular skirt of 1 mm axial depth and 0.5 mm radial thickness around its periphery.

In this second embodiment, the maximum depth of the macroprojectile 32 in the axial direction is thus 2 mm, relative to a macroprojectile diameter of 6 mm, such that the depth of the macroprojectile in the axial direction is 0.33 times the diameter of the macroprojectile. Preferably, this ratio is in the range 1.5 to 0.25, more preferably between 0.5 and 0.25. If the ratio becomes less than 0.25 it is likely that the macroprojectile will be susceptible to "cocking" upon actuation of the syringe, i.e. tilting around its diametral line, with the gas leaking past it, rather than the macroprojectile being driven down the bore 36 with the downstream face of the macroprojectile 32 perpendicular to the longitudinal axis of the bore 36.

It is thought that by making the skirt of the macroprojectile 32 sufficiently flexible the skirt can be biased radially outwardly by the action of the energy source (for example high pressure helium gas) upon operation of the syringe so as to enhance sealing between the periphery of the macroprojectile 32 and the polished bore 36 of the tubular barrel 31.

In an alternative arrangement, the upstream side of the macroprojectile 32 may, instead of being provided with a continuous annular skirt, have a non-continuous skirt, for example formed by three or more projections extending from the upstream side of the macroprojectile in the upstream direction. In the macroprojectile design illustrated in Figure 5B, four rearwardly extending projections 48 are provided on the macroprojectile 32, with only three being visible due to the sectional nature of the drawing. These projections 48 help to prevent cocking of the macroprojectile, but require less material to form them than a continuous annular skirt, thus enabling the macroprojectile to be made even lighter. To enhance stability the upstream ends of the three or more projections 48 of the Figure 5B macroprojectile might advantageously be connected together by a small annular bracing ring 49, as shown in Figure 5C.

A consequence of the macroprojectile design and material is that particles launched from the macroprojectile have been found to be launched from the syringe

at a greater velocity than the final velocity of the macroprojectile immediately prior to it impacting the macroprojectile arresting device. This is thought to be the result of a catapult effect produced by the slightly elastic piston striking the macroprojectile arresting device.

As with the first embodiment, the macroprojectile 32 in the second embodiment may have its downstream face provided with one or more topographical features to selectively retain a particle or particles on the macroprojectile. For example, the macroprojectile 32 may have a plurality of bristles integrally moulded on its downstream surface. Where a plurality of small particles (less than about 0.2 mm in diameter) are provided, these particles can simply be packed into the area surrounding the bristles. If, however, larger particles (over about 0.2 mm in diameter) are to be carried by the macroprojectile, attempts can be made to fit individual particles between adjacent bristles of a circular set of bristles, in a manner similar to that described above in conjunction with Figs. 2 and 3.

As in the first embodiment, the macroprojectile 32 of the second embodiment can additionally or alternatively be provided on its downstream face with a sputtered layer (for example, a gold layer) to counter the natural adherence of metal carrier particles to plastics materials.

To facilitate ease of placement of a macroprojectile with a particle carried thereon in the syringe, in the second embodiment the tubular barrel 31 comprises a downstream portion 31a and an upstream portion 31b. By unscrewing the tubular barrel 31 from the driver portion 34 by unscrewing the thread 33, the upstream barrel portion 31b can be removed from the oversized bore formed at the upstream end of the tubular barrel 31 and separated from the remainder of the syringe, for reasons which will now be explained.

As can most clearly be seen from Fig. 6, the upstream barrel portion 31b can be made to form part of a removable cartridge 44. This cartridge 44 further comprises macroprojectile 32, which in Fig. 6 is shown schematically as carrying a large (for example 2 mm diameter) particle 45 on its downstream surface, and a rupturable membrane 37 positioned approximately 10 mm upstream of the upstream (or rear) face of the macroprojectile 32. Advantageously, the distance between the

rupturable membrane 37 and the macroprojectile 32 is at least about 1.5 times the bore of the tubular barrel.

It will be appreciated that the provision of a removable cartridge 44 comprising at least the upstream barrel portion 31b, the macroprojectile 32 and the particle 45 simplifies use of the device. For example, after the second embodiment of needleless syringe has been operated such that the cartridge 44 is considered "spent", by unscrewing the tubular barrel 31 from the driver chamber 35 the upstream barrel portion 31b of the spent cartridge can readily be removed. In addition, the macroprojectile 32 of the spent cartridge 44 can also be removed, either by shaking it out through the upstream end of the tubular barrel 31 or by removing the macroprojectile arresting device 41. By then inserting a fresh cartridge 44 (and replacing the macroprojectile arresting device 41 if removed), the syringe can easily be made ready for re-use.

A seal (not shown) could be fitted to the front face of the upstream barrel portion 31b to protect the particle 45, which seal is removed prior to insertion of the cartridge 44 into the syringe.

In both of the illustrated embodiments, after release of driver gas from the reservoir 9, 39 into the driver chamber 5, 35 the mechanism for causing the driver gas to suddenly expand into the upstream end of the tubular barrel 1 is a rupturable membrane 7, 37. Alternative means may, however, be used, for example a fast opening valve (not shown).

A rupturing membrane has, however, been found to be a simple and effective solution. Furthermore, by providing the membrane 37 in the removable cartridge 44, a fresh rupturable membrane 37 is automatically loaded into the device when a spent cartridge is removed and a fresh cartridge inserted. In the removable cartridge arrangement disclosed in Fig. 6 of the present application, the rupturable membrane is sandwiched around its periphery between an O-ring 46 and a collar 47, which collar is attached to the main body of the upstream barrel portion 31b. Advantageously, the upstream barrel portion 31b and the collar 47 are moulded in a structural plastics material.

It will be appreciated that by changing any of the thickness, design and

material of the rupturable membrane 7, 37 the rupture pressure of the membrane can be changed. By changing the rupture pressure, the effective power of the syringe can be changed. This thus enables a range of different particle delivery profiles to be obtained from a single design of syringe simply by changing the membrane to one with a different rupture pressure. The rupturable membrane 37 may take the form of an aluminium bursting disk of less than about 100 micrometers in thickness, preferably less than 75 micrometers and more preferably less than 50 micrometers. In addition to membrane rupture pressure, other key variables which affect the power of the syringe are the length of the barrel 1, 31, the volume of the driver chamber 5, 35 and the species of gas in the reservoir 9, 39.

Fig. 7 shows a table of results obtained with the syringe of the second embodiment, with different rupturable diaphragm thicknesses and different driver chamber pressures.

In each of the tests tabulated in Fig. 7 2 mm diameter bupivicane drug particles were launched. The left hand (single) column in Fig. 7, marked "dome", indicates the result of a test conducted on a prior art movable diaphragm syringe similar to that disclosed in the abovementioned WO 96/20022 to Bellhouse et al. The five pairs of results tabulated to the right in Fig. 7 represent results achieved with a syringe very similar to that illustrated in Fig. 4, with a macroprojectile similar to that of Figures 3A and 3B. In each pair of results, the left hand column denotes the maximum velocity of the macroprojectile prior to it impacting the macroprojectile arresting device 41. The right hand column of each pair indicates the velocity at which the bupivicane particle exited the device. As mentioned earlier, it is thought that the reason for the particle exit velocity exceeding the maximum macroprojectile velocity is brought about by a catapult effect produced by the elastic macroprojectile striking the macroprojectile arresting device.

Of the five pairs of results, the number preceding the letters Al denotes the thickness of the aluminium bursting disk in micrometers. The reference to "bar" denotes the pressure of the helium within the reservoir 39. Consequently, "30 Al 45 bar" means that a 30 micrometer thick aluminium bursting disc was used with a reservoir filled with helium at a pressure of 45 bar.

Although not shown, the macroprojectile may have a composite construction, for example having a main body portion similar to the basic macroprojectile 32 construction shown in Fig. 5, with the downstream side of that main body portion being provided with cushioning material arranged to contact the macroprojectile arresting device.

Considering now the macroprojectile arresting device 41, in the second embodiment the positions of the stopping plate 42 and cushioning plate 43 are reversed and are integrally constructed as a composite single device 41. In the second embodiment, the stopping plate 42, which may be made of metal, such as stainless steel, but is preferably moulded in a structural plastics material, is positioned upstream of the cushioning plate 43. In the second embodiment this cushioning plate 43 takes the form of a rubber washer. When, in use, the syringe of the second embodiment is operated or "fired", the macroprojectile 32 will impact the strong stopping plate 42, with the impact on the stopping plate being cushioned by the cushioning plate 43. The cushioning plate 43 is held in place by the spacer 49.

The downstream portion 31a of the tubular barrel 31 may, as shown, be provided with one or more vents 48 positioned slightly upstream of the macroprojectile arresting device 41. In the Fig. 4 embodiment, two 1 mm diameter holes are positioned 2 mm upstream of the macroprojectile arresting device. The purpose of these vents 48 is to vent the pressurised driver gas from upstream of the macroprojectile once the macroprojectile comes to rest against the macroprojectile arresting device 41, making the syringe safer. By providing a sheath (not shown) around the exterior of the tubular barrel 31, and arranging for the vents 48 to vent into a silencer chamber defined between the interior of the sheath and the exterior of the tubular barrel 31, a silencing effect can be achieved.

Although in the foregoing description two separate embodiments have been disclosed, except where incompatible with one another any of the features employed in one of the embodiments may be used in the other embodiment. Similarly, in the following claims, any of the claimed features may be employed in conjunction with any of the other claimed features, except where there would be incompatibility arising.

Although the needleless syringes of the present invention have largely been described in the context of therapeutic applications, they may also be used in the delivery of diagnostics, as mentioned above.

CLAIMS

1. A needleless syringe for use in delivering a particle into target tissue of a subject, the syringe comprising:

an elongate, tubular barrel having upstream and downstream ends;

a macroprojectile received in the tubular barrel, said macroprojectile having a downstream side adapted to carry the particle to be delivered;

a macroprojectile arresting device provided at the downstream end of the barrel to arrest movement of the macroprojectile; and

an energy source for accelerating the macroprojectile along the barrel in the downstream direction upon operation of the syringe to cause the particle to be launched from the syringe when movement of the macroprojectile is arrested by the macroprojectile arresting device,

wherein said macroprojectile is injection moulded in a plastics material.

2. A needleless syringe as claimed in claim 1, wherein said macroprojectile is made substantially from a polyolefin material.

3. A needleless syringe as claimed in claim 1 or 2, wherein said macroprojectile is comprised substantially of a copolymer or homopolymer formed from polyethylene or polypropylene material.

4. A syringe as claimed in any one of the preceding claims, wherein the macroprojectile has a mass of less than about 500 mg, preferably less than about 200 mg and most preferably less than about 50 mg.

5. A syringe as claimed in any one of the preceding claims, wherein the energy source is a reservoir of compressed gas and the macroprojectile has a mass in the range of 0.5 to 1.5 times the mass of compressed gas in the reservoir.

6. A syringe as claimed in any one of the preceding claims, wherein the

macroprojectile is constructed and arranged so that when, upon operation of the syringe, the macroprojectile impacts the macroprojectile arresting device, the particle will be launched from the macroprojectile at a velocity at least equal to the velocity of the macroprojectile immediately prior to its impact with the macroprojectile arresting device.

7. A syringe as claimed in any one of the preceding claims, wherein the depth of the macroprojectile in the axial direction of the barrel is less than the diameter of the macroprojectile in the diametral direction of the barrel.

8. A syringe as claimed in claim 7, wherein the depth of the macroprojectile in the axial direction is between 1.5 and 0.25 times the diameter of the macroprojectile, preferably between 0.5 and 0.25 times the diameter of the macroprojectile.

9. A syringe as claimed in claim 8, wherein the maximum depth of the macroprojectile is less than about 5 mm and preferably less than about 3 mm.

10. A syringe as claimed in any one of the preceding claims, wherein the upstream side of the macroprojectile is recessed in its centre to provide the upstream side of the macroprojectile with a generally annular skirt around its periphery.

11. A syringe as claimed in any one of claims 1 to 9, wherein the upstream side of the macroprojectile has at least three projections extending therefrom in the upstream direction to provide the upstream side of the macroprojectile with a non-continuous skirt around its periphery.

12. A syringe as claimed in claim 10 or claim 11, wherein said skirt has a radial thickness of less than about 2 mm and preferably less than about 1 mm.

13. A syringe as claimed in any one of claims 10 to 12, wherein said

annular skirt is constructed and arranged to be biassed radially outwardly by the action of the energy source upon operation of the syringe so as to enhance sealing between the periphery of the macroprojectile and the bore of the barrel.

14. A syringe as claimed in any one of the preceding claims, wherein the downstream side of the macroprojectile either comprises a plurality of bristles to assist retention of the particle on the downstream side of the macroprojectile comprises a plated surface, or comprises both said bristles and said plated surface.

15. A syringe as claimed in any one of claims 1 to 14, wherein the macroprojectile has a composite construction.

16. A syringe as claimed in claim 15, wherein the macroprojectile has a main body portion and the downstream side of that main body portion is provided with cushioning material and is arranged to contact the macroprojectile arresting device.

17. A needleless syringe for use in delivering a particle into target tissue of a subject, the syringe comprising:

an elongate, tubular barrel having upstream and downstream ends;

a macroprojectile received in the tubular barrel, said macroprojectile having a downstream side adapted to carry the particle to be delivered;

a macroprojectile arresting device provided at the downstream end of the barrel to arrest movement of the macroprojectile; and

an energy source for accelerating the macroprojectile along the barrel in the downstream direction upon operation of the syringe to cause the particle to be launched from the syringe when movement of the macroprojectile is arrested by the macroprojectile arresting device,

wherein the downstream side of the macroprojectile either comprises a plurality of bristles to assist retention of the particle on the downstream side of the macroprojectile, comprises a plated surface to assist separation of the particle from

the downstream side of the macroprojectile, or comprises both said bristles and said plated surface.

18. A syringe as claimed in claim 14 or claim 17, wherein the plated surface is a gold plated surface.

19. A syringe as claimed in any one of claims 14, 17 and 18, wherein the bristles are integrally moulded with the main body of the macroprojectile.

20. A syringe as claimed in any one of the preceding claims, further comprising a particle carried on the downstream side of the macroprojectile, wherein said particle is of the order of 2 mm diameter.

21. A syringe as claimed in any one of claims 1 to 19, further comprising a particle carried on the downstream side of the macroprojectile, wherein the diameter of said particle is less than about 0.2 mm.

22. A syringe as claimed in claim 21, wherein the diameter of said particle is less than about 10 μm.

23. A syringe as claimed in any one of the preceding claims,

wherein the macroprojectile arresting device is provided with a cushioning portion to cushion deceleration of the macroprojectile upon its impact with the macroprojectile arresting device.

24. A syringe as claimed in claim 23, wherein the cushioning portion is constructed and arranged to keep the maximum deceleration of the macroprojectile below about 10^8 m/s^2 when the velocity of the macroprojectile upon its impact with the macroprojectile arresting device is of the order of 400 m/s.

25. A syringe as claimed in claim 23 or 24, wherein the macroprojectile

arresting device is further provided with a relatively rigid stopping portion, with the cushioning portion being arranged to be compressed upon macroprojectile impact.

26. A syringe as claimed in claim 25, wherein the stopping portion comprises a generally annular element made of metal.

27. A syringe as claimed in claim 25, wherein the stopping portion and the cushioning portion are integral.

28. A syringe as claimed in claim 27, wherein the stopping portion and the cushioning portion are integrally moulded in a structural plastics material.

29. A syringe as claimed in any one of claims 23 to 26, wherein the cushioning portion comprises a generally annular element formed from elastomeric material.

30. A syringe as claimed in any one of the preceding claims, wherein the macroprojectile arresting device is releasably attached to the downstream end of the barrel.

31. A syringe as claimed in any one of the preceding claims,

wherein the barrel comprises an upstream portion and a downstream portion, the upstream portion being separable from the downstream portion, and the macroprojectile is provided in the form of a removable cartridge comprising at least the macroprojectile and the upstream barrel portion.

32. A needleless syringe for use in delivering a particle into target tissue of a subject, the syringe comprising:

an elongate, tubular barrel having upstream and downstream ends;

a macroprojectile received in the tubular barrel, said macroprojectile having a downstream side adapted to carry the particle to be delivered;

a macroprojectile arresting device provided at the downstream end of the barrel to arrest movement of the macroprojectile; and

an energy source for accelerating the macroprojectile along the barrel in the downstream direction upon operation of the syringe to cause the particle to be launched from the syringe when movement of the macroprojectile is arrested by the macroprojectile arresting device,

wherein the barrel comprises an upstream portion and a downstream portion, the upstream portion being separable from the downstream portion, and further wherein the macroprojectile is provided in the form of a removable cartridge comprising at least the macroprojectile and the upstream barrel portion.

33. A syringe as claimed in claim 31 or claim 32, wherein the removable cartridge further comprises a rupturable membrane positioned between the macroprojectile and the energy source, said rupturable membrane being adapted to be ruptured by the energy source upon operation of the syringe.

34. A syringe as claimed in claim 33, wherein the rupturable membrane is provided towards the upstream end of the upstream barrel portion and the macroprojectile is provided towards the downstream end of the upstream barrel portion.

35. A syringe as claimed in claim 33 or 34, wherein the rupturable membrane and the macroprojectile are positioned apart by a distance at least about 1.5 times the bore of the tubular barrel.

36. A syringe as claimed in any one of claims 33 to 35, wherein the rupturable membrane is an aluminium bursting disc.

37. A syringe as claimed in claim 36, wherein the aluminium bursting disc is of less than about 100 μm in thickness, preferably less than 75 μm and more preferably less than 50 μm.

38. A syringe as claimed in any one of claims 31 to 37, wherein the syringe is reusable after a first operation.

39. A syringe as claimed in claim 38, wherein the syringe is readied for reuse after a first operation by removal of a spent said cartridge and insertion of a fresh cartridge comprising at least a fresh said macroprojectile and a fresh said upstream barrel portion.

40. A syringe as claimed in any one of the preceding claims, wherein said particle comprises a drug, vaccine or diagnostic agent.

41. A syringe as claimed in any one of claims 1 to 39, wherein said particle comprises a carrier particle coated with a genetic material.

42. A syringe as claimed in any one of the preceding claims, wherein the energy source comprises a gas reservoir filled with pressurised gas that is capable of being opened to deliver pressurised gas suddenly to the upstream end of the barrel to accelerate the macroprojectile down the barrel.

43. A syringe as claimed in claim 42, wherein the reservoir has a capacity of less than about 10 ml and more preferably less than about 5 ml.

44. A syringe as claimed in claim 42, wherein the macroprojectile is arranged, in use, to sweep the volume of the tubular barrel and the reservoir has a capacity of less than 5 times, preferably less than 2 times, the swept volume of the tubular barrel.

45. A syringe as claimed in any one of claims 42 to 44, wherein the gas reservoir is filled with pressurised gas at a pressure of less than about 100 bar, preferably less than about 70 bar and more preferably less than about 50 bar.

46. A syringe as claimed in any one of the preceding claims, wherein the bore of the barrel is less than about 25 mm diameter, preferably less than about 10 mm and more preferably less than about 7 mm.

47. A syringe as claimed in any one of the preceding claims, wherein the barrel is provided with at least one lateral vent upstream of its downstream end to allow ventilation of the barrel upstream of the macroprojectile after operation of the syringe.

48. A syringe as claimed in claim 47, wherein the syringe further comprises a silencer.

49. A syringe as claimed in claim 48 wherein said silencer comprises a chamber, and the at least one lateral vent is arranged to vent the bore of the barrel into said chamber.

50. A cartridge for use in a needleless syringe, said cartridge comprising:
a cartridge barrel section having a bore;
a macroprojectile received in the bore of the cartridge barrel section; and
a particle releasably carried on a downstream face of the macroprojectile.

51. A cartridge as claimed in claim 50, wherein the needleless syringe comprises a downstream barrel section having a bore and upstream and downstream ends, an arresting device provided at the downstream end of that downstream barrel section, and an energy source,

and wherein the cartridge barrel section is adapted to be inserted, in use, into the syringe with the downstream end of the bore of the cartridge barrel section contiguous with the upstream end of the bore of the downstream barrel section of the syringe, whereby, in use and upon operation of the syringe, the energy source may be used to displace the macroprojectile from the cartridge barrel section into the downstream barrel section of the syringe and to accelerate the macroprojectile along

the downstream barrel section to impact the arresting device with sufficient velocity as to cause said particle to be launched from the syringe, when movement of the macroprojectile is arrested by the arresting device, with sufficient velocity as to be delivered into target tissue of a subject.

52. A cartridge as claimed in claim 50 or claim 51, further comprising a rupturable membrane positioned upstream of the macroprojectile.

53. A cartridge as claimed in any one of claims 50 to 52, wherein the rupturable membrane and the macroprojectile are positioned apart by a distance between about 1.5 and 3 times the bore of the tubular barrel.

54. A cartridge as claimed in claim 52 or claim 53, wherein the rupturable membrane is an aluminium bursting disc.

55. A cartridge as claimed in claim 54, wherein the aluminium bursting disc is of less than about 100 μm in thickness, preferably less than 75 μm and more preferably less than 50 μm.

56. A cartridge as claimed in any one of claims 50 to 55, wherein the particle comprises a drug, vaccine or diagnostic agent.

57. A cartridge as claimed in any one of claims 50 to 55, wherein the particle comprises a carrier particle coated with a genetic material.

58. A cartridge as claimed in any one of claims 50 to 57, wherein said macroprojectile is made substantially from a polyolefin material.

59. A cartridge as claimed in any one of claims 50 to 58, wherein said macroprojectile is injection moulded.

60. A cartridge as claimed in claim 58, wherein said macroprojectile is comprised substantially of a copolymer or homopolymer formed from polyethylene or polypropylene material.

61. A cartridge as claimed in any one of claims 50 to 60, wherein the energy source is a reservoir of compressed gas and the macroprojectile has a mass in the range of 0.5 to 1.5 times the mass of compressed gas in the reservoir.

62. A cartridge as claimed in any one of claims 50 to 61, wherein the depth of the macroprojectile in the axial direction of the barrel is less than the diameter of the macroprojectile in the diametral direction of the cartridge barrel section.

63. A cartridge as claimed in claim 62, wherein the maximum depth of the macroprojectile is less than about 5 mm and preferably less than about 3 mm.

64. A cartridge as claimed in any one of claims 50 to 63, wherein the upstream side of the macroprojectile is recessed in its centre to provide the upstream side of the macroprojectile with a generally annular skirt around its periphery.

65. A cartridge as claimed in claim 64, wherein the annular skirt has a radial thickness of less than about 2 mm and preferably less than about 1 mm.

66. A cartridge as claimed in claim 64, wherein the annular skirt has a radial thickness of less than about one quarter of the diameter of the macroprojectile in the diametral direction of the cartridge barrel section.

67. A cartridge as claimed in any one of claims 50 to 66, further comprising a rupturable membrane.

68. A cartridge as claimed in claim 67, wherein said rupturable membrane

is located upstream of said macroprojectile and spans said bore.

69 A cartridge as claimed in any one of claims 50 to 68, wherein the downstream end of said bore and said macroprojectile are arranged so as, in use, to enable the macroprojectile to pass out the downstream end into a needleless syringe.

70 A cartridge as claimed in claim 69, wherein said macroprojectile can freely exit said bore upon application of gaseous energy to its upstream face.

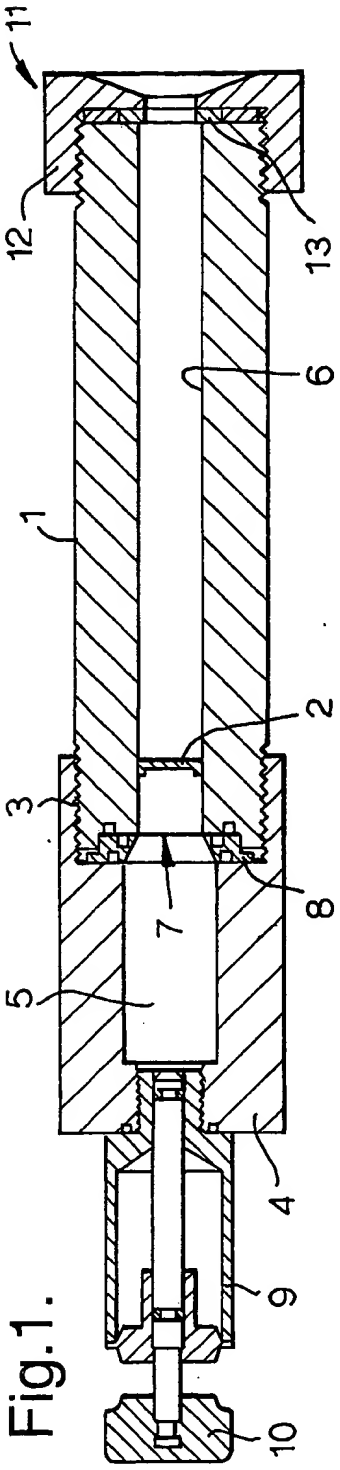


Fig.1.

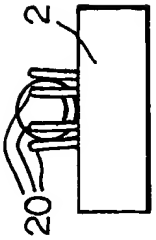


Fig.3B.

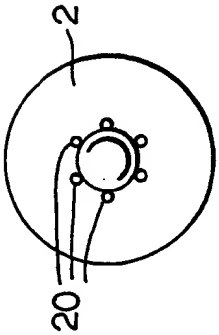


Fig.3A.

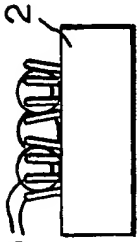


Fig.2B.

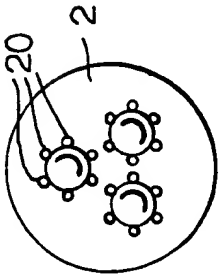


Fig.2A.

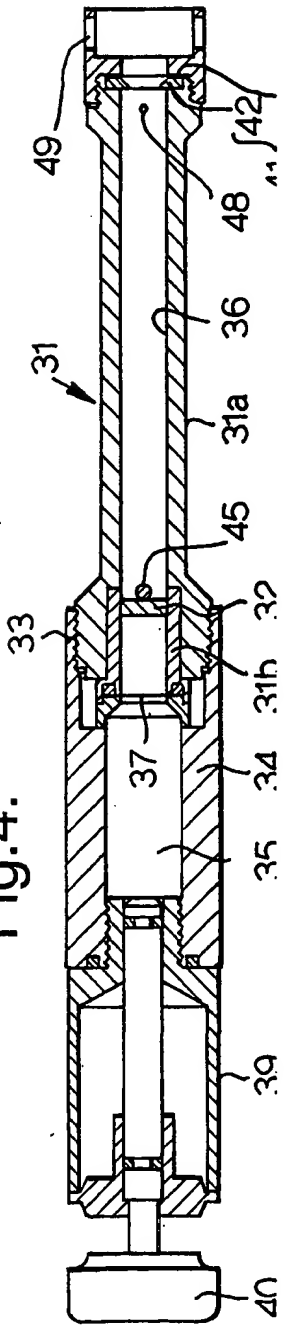


Fig.4.

Fig.5A.

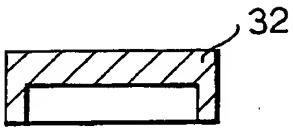


Fig.5B.

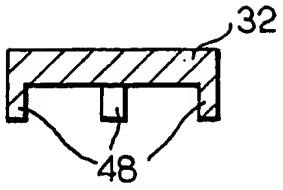


Fig.5C.

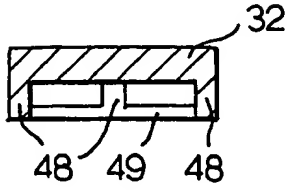


Fig.6.

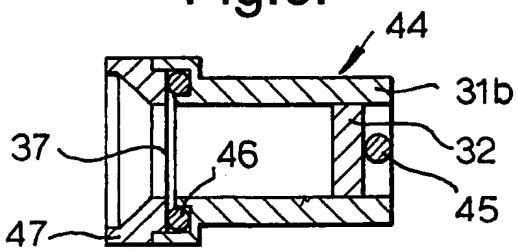
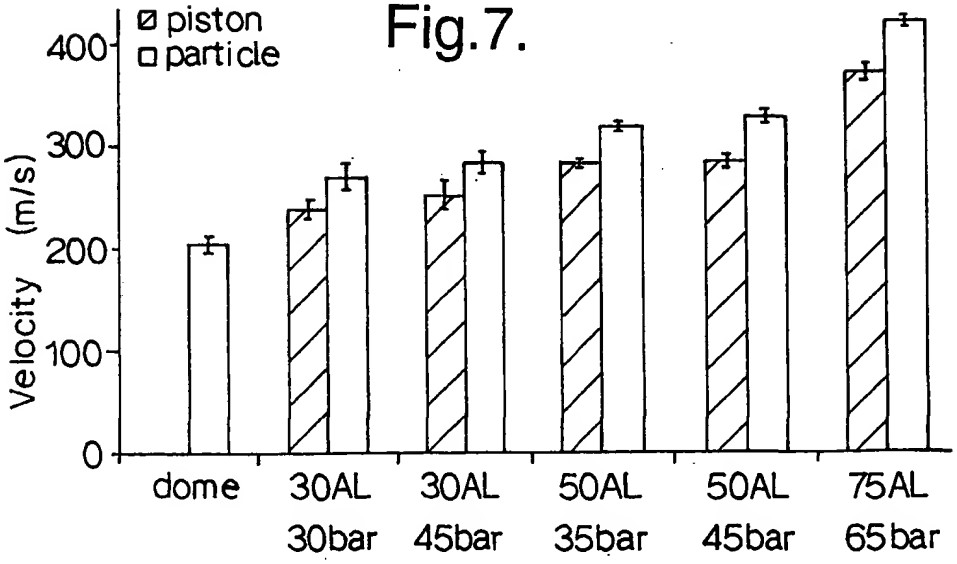


Fig.7.



INTERNATIONAL SEARCH REPORT

Inte nal Application No
PC1/GB 01/03285

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/30 C12M3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M C12M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2001	29/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sedy, R

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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